


DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 336, 338, and 341

[Docket No. 97N-0128]

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Labeling of Diphenhydramine-Containing Drug Products for Over-the-Counter Human Use

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule amending the final monographs for over-the-counter (OTC) antiemetic, antihistamine, antitussive, and nighttime sleep-aid drug products to add a warning statement for oral products containing diphenhydramine citrate or diphenhydramine hydrochloride. The warning advises consumers not to use oral OTC diphenhydramine products with any other product containing diphenhydramine, including products used topically. This final rule also includes the agency's conclusions on additional warning statements and a direction statement for OTC external analgesic drug products containing diphenhydramine hydrochloride. These conclusions will be incorporated into the final monograph for OTC external analgesic drug products in a future issue of the **Federal Register**. FDA is issuing this final rule after considering public comments on the agency's proposed regulation and all new data and information on drug products containing diphenhydramine that have come to the agency's attention.

cd01181

DATES:

Effective Date: This regulation is effective [*insert date 12 months after date of publication in the **Federal Register***].

Compliance Dates: The compliance date for oral products with annual sales less than \$25,000 is [*insert date 24 months after date of publication in the **Federal Register***]. The compliance date for all other oral products is [*insert date 12 months after date of publication in the **Federal Register***].

FOR FURTHER INFORMATION CONTACT: Michael T. Benson, Center for Drug Evaluation and Research (HFD-560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-2222.

SUPPLEMENTARY INFORMATION:**I. Background**

In the **Federal Register** of August 29, 1997 (62 FR 45767), FDA published a notice of proposed rulemaking to amend the tentative final monograph (TFM) for OTC external analgesic drug products (proposed 21 CFR 348.50(c)(10)) to add the following warning statement for diphenhydramine hydrochloride: “Do Not Use:” (these three words in bold print) “on chicken pox, poison ivy, sunburn, large areas of the body, broken, blistered, or oozing skin, more often than directed, or with any other product containing diphenhydramine, even one taken by mouth.” The agency also proposed to amend the final monographs for OTC antiemetic (proposed 21 CFR 336.50(c)(8)), antihistamine (proposed 21 CFR 341.72(c)(6)(iv) and (c)(7)) and antitussive (proposed 21 CFR 341.74(c)(4)(viii)(C) and (c)(4)(ix)(C)), and nighttime sleep-aid (proposed 21 CFR 338.50(c)(5)) drug products to add the following warning statement for diphenhydramine ingredients: “Do Not Use” (these three words in bold print)

“with any other product containing diphenhydramine, including one applied topically.” The agency proposed these warnings based on reports of adverse events when oral and topical diphenhydramine products were used concurrently. In response to that proposal, two manufacturers and a marketing association submitted comments. The agency is responding to those comments and publishing a final rule that applies to oral diphenhydramine products now and to topical diphenhydramine products at a future date.

Twenty-four months after the date of publication in the **Federal Register**, for oral diphenhydramine-containing products with sales less than \$25,000, and 12 months after the after the date of publication in the **Federal Register**, for all other such oral products, no OTC drug product that is subject to this final rule and that contains a nonmonograph condition may be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved new drug application or abbreviated new drug application. Further, any OTC drug product subject to this final rule that is repackaged or relabeled after the compliance dates of the final rule must be in compliance with the applicable monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily as soon as possible.

II. The Agency’s Conclusion on the Comments

(Comment 1) One comment contended that the proposed label changes for diphenhydramine products are not necessary and would have no significant impact. The comment stated that the 23 reported cases of toxicity between 1979 and 1989 discussed in the proposal (62 FR 45767 at 45768) are minute compared to the millions of applications of these topical products. Further,

in all cases, the toxicity was due to consumer noncompliance with directions and indications. In the majority of cases, no treatment was required except for discontinuance of the drug, with affected consumers released from medical care in 24 hours. The comment concluded that additional warnings would have no effect on consumers who have obviously ignored the existing warnings.

The agency disagrees. The agency recognizes that the number of reports is small compared to the total doses used. However, there is particular concern because of the reports of toxic psychosis, especially in children, discussed in the proposed rule. There is also concern of underreporting because there is no current reporting requirement for topical diphenhydramine products marketed under the proposed OTC drug monograph. As pointed out in the proposal (62 FR 45767 at 45769), a major manufacturer voluntarily revised the warnings for its topical diphenhydramine products after receiving adverse reaction reports. The agency concludes that additional labeling information should help reduce possible misuse of these products and reduce the possibility of serious adverse reactions.

As noted, our decision to require the warning set forth in this final rule is based on other comments made in response to the proposed rule and our analysis of numerous adverse event reports that document the potential health risks associated with the concurrent use of OTC drug products that contain diphenhydramine. Mandating a warning does not require a finding that any or all of the OTC drug products that contain diphenhydramine actually caused an adverse event, and FDA does not so find. Nor does FDA's mandate of a warning repudiate the OTC drug monographs under which the affected drug products have been lawfully marketed. Rather, as a consumer protection

agency, FDA has determined that this additional warning is necessary to ensure that these OTC drug products continue to be safe and effective for their labeled indications under ordinary conditions of use as those terms are defined in the Federal Food, Drug, and Cosmetic Act. This judgment balances the benefits of these drug products against their potential risks, and reflects our conclusion that even a potential link between the overuse of diphenhydramine and serious adverse health consequences warrants this action (see 21 CFR 330.10(a)).

FDA's decision to act in an instance such as this one need not meet the standard of proof required to prevail in a private tort action (*Glastetter v. Novartis Pharmaceuticals, Corp.*, 252 F. 3d 986, 991 (8th Cir. 2001)). To mandate a warning, or take similar regulatory action, FDA need not show, nor do we allege, actual causation.

The distinction between avoidance of risk through regulation and compensation for injuries after the fact is a fundamental one. In the former, risk assessments may lead to control of a toxic substance even though the probability of harm to any individual is small and the studies necessary to assess the risk are incomplete; society as a whole is willing to pay the price as a matter of policy. In the latter, a far higher probability (greater than 50%) is required since the law believes it is unfair to require an individual to pay for another's tragedy unless it is shown that it is more likely than not that he caused it * * * .

In re "Agent Orange" Product Liability Litigation, 597 F. Supp. 740, 781 (E.D.N.Y. 1984), *aff'd.*, 818 F. 2d 145 (2d Cir. 1987) at 781. In making its decision, the agency follows "the preventive perspective that [] agencies adopt in order to reduce public exposure to harmful substances." *Glastetter*, 252 F.3d at 991, *quoting Hollander v. Sandoz Pharmaceuticals, Corp.*, 95 F. Supp.2d 1230, 1234 n. 9 (W.D. Okla. 2000). This is what we have done here.

(Comment 2) Two comments contended that OTC topical diphenhydramine products indicated for “pain and itch of sunburn and poison ivy” should not be contraindicated for the same uses and that the agency’s proposed warning could confuse consumers. The comments added that the proposed labeling could be interpreted to mean that usage on large areas of the body is permitted as long as the product is not used more than three to four times daily. One comment stated that the proposal only cited two reports of toxicity when the drug was applied topically to a widespread area of intact sunburned skin and to a severe case of poison ivy. There were no reported cases when the drug was applied on limited areas of skin compromised with poison ivy or sunburn. The comment recommended that the labeling state “do not use more often than directed,” and that this part of the warning be moved to “Directions” because the statement relates to dosing.

Another comment agreed that topical diphenhydramine products should not be used on large areas of skin either intact or with open lesions. However, it objected to warning against use on damaged skin conditions, specifically broken, blistered, or oozing skin, contending that such labeling may confuse consumers seeking use for skin conditions such as minor cuts, minor burns, or insect bites that are characterized by broken, blistered, or oozing skin. Further, the comment was unable to find any adverse event cases reported when the product was applied according to the labeled directions on limited areas of damaged skin. A second comment also was unable to find any adverse reports associated with use on limited areas of damaged skin. It noted the cited cases in the proposal concerned application on compromised skin over a large skin surface. The comment suggested that this problem is best addressed by the warning against use “on large areas of the body.”

The agency agrees that topical diphenhydramine products should be indicated for use on limited areas of skin with poison ivy or sunburn and that the warning is intended to alert consumers not to use these products over large areas of the body or more often than directed for any condition. Because sunburn, poison ivy, and other conditions for which topical diphenhydramine is used (e.g., minor cuts and burns, and insect bites) could be characterized by “broken, blistered, or oozing skin,” the agency is removing these conditions from the proposed warning.

Since the proposal was published, the agency has established a new labeling format for all OTC drug products (see section III in this document). That labeling format conveys information in a segmented manner. Based on the new labeling format and the revisions described in the previous paragraph, the information in the final warning for topical products would now appear as follows: “Do not use [bullet] on large areas of the body [bullet] with any other product containing diphenhydramine, even one taken by mouth,” “Ask a doctor before use [bullet] on chicken pox [bullet] on measles,” and under “Directions [bullet] do not use more often than directed.” The proposed monograph directions for external analgesic drug products containing diphenhydramine are “Apply to affected area not more than 3 to 4 times daily.” The agency concludes that the revised warnings and directions should be clearer and more understandable to consumers.

(Comment 3) One comment recommended changing “Do not use on chicken pox” to “Do not use on chicken pox, except as directed by a physician.” The comment cited additional toxicity reports not included in the proposed rule in which diphenhydramine was applied liberally on children with large areas of chicken pox. However, the comment stated that since

physicians may find use appropriate in select cases, consumers should be advised to consult their physicians. Another comment agreed because a doctor may advise use on a few itchy spots to help prevent scratching and the scarring that could result.

One comment from a manufacturer proposed that “measles” be included because a case of diphenhydramine toxicity after treatment with diphenhydramine for measles had been reported to the company. The comment noted that the adverse event was similar to the chicken pox cases discussed in the proposed rule, and that both chicken pox and measles may appear as a widespread rash. Another comment concurred and proposed the following: “Ask a doctor before use on chicken pox or measles.”

The agency agrees. In the proposal, the agency stated that because none of the case reports was associated with measles, that condition was not specifically listed in the warning (62 FR 45767 at 45771). The agency invited comments related to any adverse events associated with the topical application of diphenhydramine to measles. As there has been at least one measles case report and since chicken pox and measles may appear similar to consumers, the agency is including both conditions in product labeling. The agency did not receive any comments opposed to including measles in labeling. When the monograph for OTC external analgesic drug products becomes final, it will contain the following warning for topical diphenhydramine products: “Ask a doctor before use [bullet] on chicken pox [bullet] on measles.”

(Comment 4) Two comments agreed that it was reasonable to add a warning to the labeling of OTC oral diphenhydramine products. The comments recommended revising the last part of the agency’s proposed warning from “including one applied topically” to “even one used on skin” for two reasons.

First, the revised language comprises six syllables in five words instead of nine syllables in four words, making it easier to read. Second, consumers who do not understand the meaning of the word “topically” are more likely to know what is meant by “on skin.”

The agency agrees and has revised the labeling for OTC diphenhydramine oral products to read: “Do not use: [bullet] with any other product containing diphenhydramine, even one used on skin.”

(Comment 5) One comment expressed concern over the cost of implementing the new labeling for a small manufacturer of topical products and contended: (1) The proposed labeling is an example of the type of regulation that Executive Order 12866 and the Regulatory Flexibility Act were intended to eliminate; (2) the cost to relabel would be substantially more than the \$2,000 to \$3,000 the agency mentioned in the proposal because of ordering requirements for tubes and boxes and a low dollar volume of annual sales; (3) existing inventory would have to be destroyed because it would not be used prior to the effective date for new labeling; and (4) there would be excessive costs associated with producing new graphics for labeling all products. The comment did not provide any specific data or figures to support its cost speculation.

The agency disagrees that the proposed labeling is an example of the type of regulation that Executive Order 12866 and the Regulatory Flexibility Act were intended to eliminate. The agency has determined that the additional warning statement is necessary for the safe and effective use of OTC drug products that contain diphenhydramine. The proposed rule (62 FR 45767 at 45772 to 45773) and this final rule (section V of this document) examine the

impacts of the rule under Executive Order 12866 and the Regulatory Flexibility Act.

The \$2,000 to \$3,000 relabeling cost stated by the agency in the proposal (62 FR 45767 at 45772) was based on information that the agency obtained from various drug manufacturers, both small and large. That relabeling cost included the cost associated with producing new graphics for labeling products and the cost of tubes and boxes on which the labeling would be printed.

The agency does not anticipate that significant existing inventory would have to be destroyed because it would not be used prior to the effective date for new labeling. It has been almost 5 years since the proposed rule was published, and existing inventory should have been reduced during this time. In addition, manufacturers still have adequate time to deplete existing stocks of inventory. This final rule has a compliance date of 24 months after its publication in the **Federal Register** for oral products containing diphenhydramine citrate or diphenhydramine hydrochloride with annual sales less than \$25,000, and a compliance date of 12 months after its publication in the **Federal Register** for all other oral products. The monograph for topical (external analgesic) drug products containing diphenhydramine [products in tubes] is not yet final and, when issued, will specify the time by which relabeling is required. Manufacturers of topically applied diphenhydramine products are encouraged to implement the new labeling at an earlier date should they need to order additional labeling for their products before the agency issues the final monograph for OTC external analgesic drug products.

Since the proposal was published in 1997, the agency issued a final rule on March 17, 1999 (64 FR 13254) establishing a new standardized labeling format and content for all OTC drug products (the 1999 final rule). That final

rule contained an extensive discussion of the costs of relabeling OTC drug products, including the impact on small businesses (64 FR 13254 at 13284 to 13285). In an effort to reduce the economic impact on small businesses, the agency generally provides an additional 12 months of compliance time for relabeling of OTC drug products with annual sales less than \$25,000 which is being provided for oral diphenhydramine drug products in this final rule.

III. New Labeling Format

In the 1999 final rule, the agency established standardized format and standardized content requirements for the labeling of OTC drug products set forth in § 201.66 (21 CFR 201.66). The requirements relate to the labeling for diphenhydramine-containing OTC drug products by including bullets prior to certain words under the “Warnings” subheadings “Do not use” and “Ask a doctor before use” and prior to the direction “do not use more often than directed.” The subheadings are highlighted in bold type in accordance with § 201.66(c)(5). Pertinent parts of the new labeling are in tables 1 and 2 of this document.

TABLE 1.—WARNING FOR ORAL ANTIEMETIC, ANTIHISTAMINE, ANTITUSSIVE, AND NIGHTTIME SLEEP-AID DRUG PRODUCTS CONTAINING DIPHENHYDRAMINE INGREDIENTS

<i>Warnings</i>
Do not use • with any other product containing diphenhydramine, even one used on skin

TABLE 2.—WARNINGS AND DIRECTION FOR EXTERNAL ANALGESIC DRUG PRODUCTS CONTAINING DIPHENHYDRAMINE INGREDIENTS

<i>Warnings</i>
• For external use only
Do not use • on large areas of the body • with any other product containing diphenhydramine, even one taken by mouth
Ask a doctor before use • on chicken pox • on measles
Directions • do not use more often than directed

IV. The Agency's Final Conclusions

Based on the available evidence, the agency is issuing a final rule amending the final monographs for orally administered OTC antiemetic, antihistamine, antitussive, and nighttime sleep-aid drug products containing diphenhydramine to include the new warning in table 1 of this document. This final rule also discusses new warnings and a direction in table 2 of this document that will be incorporated into the final monograph for OTC external analgesic drug products in a future issue of the **Federal Register**, when the complete monograph for those products is published.

V. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, if a rule has a significant economic impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of the rule on small entities. Section 202(a) of the Unfunded Mandates Reform Act requires that agencies prepare a written statement and economic analysis before proposing any rule that may result in an expenditure in any one year by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million (adjusted annually for inflation).

The agency concludes that this final rule is consistent with the principles set out in the Executive order and in these two statutes. The final rule is not a significant regulatory action as defined by the Executive order and so is not subject to review under the Executive order. As discussed in this section, FDA has determined that this final rule will not have a significant economic impact on a substantial number of small entities. The Unfunded Mandates Reform Act does not require FDA to prepare a statement of costs and benefits for this final rule because the final rule is not expected to result in any 1-year expenditure that would exceed \$100 million adjusted for inflation. The current inflation adjusted statutory threshold is about \$110 million.

The purpose of this final rule is to add the same warning statement for four categories of OTC drugs in three different OTC drug monographs that include products containing diphenhydramine taken orally. Based on information in the agency's drug listing system (DLS), there are approximately 95 manufacturers, 59 repackers, and 247 distributors of about 800 to 1,000 oral diphenhydramine products. The agency does not believe these companies would need to increase the package size to add this warning and, thus, they should incur only minor costs to relabel their products. The agency believes that relabeling costs of the type required by this final rule generally average about \$2,000 to \$3,000 per stock keeping unit (SKU) (individual products, packages, and sizes). Assuming that there are about 800 to 1,000 affected SKUs in the marketplace, total one-time costs of relabeling would be \$1.6 million (\$2,000 per SKU x 800 SKUs) to \$3 million (\$3,000 per SKU x 1,000 SKUs). The agency believes the actual cost would be lower because most of the labeling changes will be made by private label manufacturers that tend to use simpler and less expensive labeling.

Manufacturers of oral diphenhydramine-containing products will incur most of the costs associated with this final rule. The impact on any one firm will vary based on the number and types of products that need relabeling. About 85 percent of the manufacturers meet the Small Business Administration's definition of a small entity (fewer than 750 employees). In the proposal (62 FR 45767 at 45772 to 45773), the agency estimated that the proposed rule may have a significant impact on some small entities. On further analysis, the agency now believes that the final rule will not have a significant impact on a substantial number of small entities because about one-half of the firms have listed only one diphenhydramine-containing product with the agency, another 30 percent have listed two or three products, and all of the manufacturers produce a number of other OTC drug products not affected by this rule. The agency does not believe the cost to any one firm to relabel its products subject to this final rule will approach 1 percent of the entity's income.

The DLS also identifies approximately 30 manufacturers, 4 repackers, and 53 distributors of about 100 topical diphenhydramine products. The cost for these companies to relabel their products will be discussed in the final monograph for OTC external analgesic drug products.

The agency considered but rejected several alternatives: (1) A shorter or longer implementation period, and (2) an exemption from coverage for small entities. While the agency believes that consumers would benefit from having this new labeling in place as soon as possible, the agency also acknowledges that a shorter implementation period could significantly increase the compliance costs and these costs could be passed through to consumers. A longer time period would unnecessarily delay the benefit of new labeling to

consumers who self-medicate with these OTC antiemetic, antihistamine, antitussive, and nighttime sleep-aid drug products. The agency rejected an exemption for small entities because the new labeling is also needed by consumers who purchase products marketed by those entities. However, a longer compliance date until 24 months after date of publication in the **Federal Register** is being provided for products with annual sales less than \$25,000.

For the reasons in this section and under the Regulatory Flexibility Act (5 U.S.C. 605(b)), the agency certifies that this final rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

VI. Paperwork Reduction Act of 1995

FDA concludes that the labeling requirements in this document are not subject to review by the Office of Management and Budget because they do not constitute a “collection of information” under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*) Rather, the labeling statements are a “public disclosure of information originally supplied by the Federal government to the recipient for the purpose of disclosure to the public” (5 CFR 1320.3(c)(2)).

VII. Environmental Impact

The agency has determined under 21 CFR 25.31(a) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VIII. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency has concluded that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

List of Subjects in 21 CFR Parts 336, 338, and 341

Labeling, Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 336, 338, and 341 are amended as follows:

PART 336—ANTIEMETIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

1. The authority citation for 21 CFR part 336 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

2. Section 336.50 is amended by adding paragraph (c)(8) to read as follows:

§ 336.50 Labeling of antiemetic drug products.

* * * * *

(c) * * *

(8) *For products containing diphenhydramine hydrochloride identified in § 336.10(c). “Do not use [bullet]¹ with any other product containing diphenhydramine, including one used on skin”.*

* * * *

PART 338—NIGHTTIME SLEEP-AID DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

3. The authority citation for 21 CFR part 338 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

4. Section 338.50 is amended by adding paragraph (c)(5) to read as follows:

§ 338.50 Labeling of nighttime sleep-aid drug products.

* * * *

(c) * * *

(5) “Do not use [bullet]¹ with any other product containing diphenhydramine, even one used on skin”.

* * * *

PART 341—COLD, COUGH, ALLERGY, BRONCHODILATOR, AND ANTI-ASTHMATIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

5. The authority citation for 21 CFR part 341 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

6. Section 341.72 is amended by adding paragraphs (c)(6)(iv) and (c)(7) as follows:

¹ See § 201.66(b)(4) of this chapter for definition of bullet symbol.

¹ See § 201.66(b)(4) of this chapter for definition of bullet symbol.

§ 341.72 Labeling of antihistamine drug products.

* * * *

(c) * * *

(6) * * *

(iv) *For products containing diphenhydramine citrate or diphenhydramine hydrochloride identified in § 341.12(f) and (g).* “Do not use [bullet]¹ with any other product containing diphenhydramine, even one used on skin”.

(7) *For products containing diphenhydramine citrate or diphenhydramine hydrochloride identified in § 341.12(f) and (g).* “Do not use [bullet] with any other product containing diphenhydramine, even one used on skin”.

* * * *

7. Section 341.74 is amended by adding paragraphs (c)(4)(viii)(C) and (c)(4)(ix)(C) to read as follows:

§ 341.74 Labeling of antitussive drug products.

* * * *

(c) * * *

(4) * * *

(viii) * * *

(C) “Do not use [bullet]¹ with any other product containing diphenhydramine, even one used on skin”.

* * * *

(ix) * * *

¹ See § 201.66(b)(4) of this chapter for definition of bullet symbol.

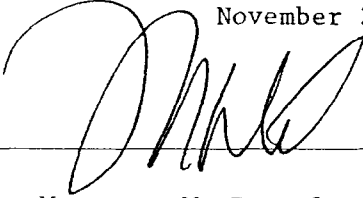
¹ See § 201.66(b)(4) of this chapter for definition of bullet symbol.

(C) "Do not use [bullet] with any other product containing
diphenhydramine, even one used on skin".

* * * * *

Dated: 11-25-02

November 25, 2002.



Margaret M. Dotzel,
Assistant Commissioner for Policy.

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